

## Communications to the Editor

### A Novel and Expedient Reduction of Tertiary Amides to Aldehydes Using $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$

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Functional group manipulations continue to play an important role in organic synthesis, and hence the development of new methods to carry out these transformations remains an important part of organic chemistry. The reduction of amides to aldehydes is one such transformation, and although several methods are available,<sup>1</sup> many are substrate specific,<sup>2</sup> the outcome of the reaction being dependent upon the nature of the nitrogen substituent. Problems with existing techniques, which generally require the use of highly reactive reagents such as aluminum and boron hydrides, include low functional group tolerance, over-reduction to amines or alcohols, or the formation of other byproducts. Herein, we report a general procedure for the conversion of tertiary amides to aldehydes, which employs a commercially available reagent,  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  (Schwartz reagent<sup>3</sup>) and operates under mild conditions at room temperature (Scheme 1).

As detailed in Table 1, both aromatic (including heteroaromatic) and aliphatic tertiary amides can be reduced by  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ . Furthermore, a variety of tertiary amides, including dialkyl; methoxymethyl (Weinreb's amide); and even Evans' *N*-acyl oxazolidinone<sup>4</sup> can be reduced directly to the corresponding aldehyde. Electron-withdrawing groups such as the *p*-nitro group (entry 9) and electron-donating groups such as *p*-methoxy group (entry 10) do not effect the reduction appreciably. The cyano functionality (entries 7 and 8), which is known to be reduced after extended time in the presence of  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  remains intact, presumably due to the kinetically slow rate of reduction of the cyano as compared to the amide reduction.<sup>5</sup> Entry 8 illustrates the use of commercially available deuterated Schwartz reagent to provide the corresponding deuterated aldehyde.

As the Schwartz reagent is perhaps best known for its ability to reduce alkenes and alkynes,<sup>6</sup> one example was examined (entry 6) in which the substrate contained a double bond. The aldehyde was obtained selectively in 87% yield. In this case, however, 12% of the corresponding allylic alcohol was also formed. It must also be noted that the ketone functionality was reduced (entry 13) to the corresponding alcohol as well as providing amide reduction. This reduction was somewhat surprising as acetophenone is known to be unreactive toward the Schwartz reagent.<sup>7</sup> This reduction was then presumed to be favored due to the electron-

**Table 1.**  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ -Mediated Conversion of Amides to Aldehydes

| Entry          | Amide | Product | Time (min) | Yield (%)       |
|----------------|-------|---------|------------|-----------------|
| 1              |       |         | 15         | 96              |
| 2              |       |         | 20         | 93              |
| 3              |       |         | 15         | 82              |
| 4              |       |         | 15         | 90              |
| 5              |       |         | 15         | 99              |
| 6              |       |         | 15         | 87 <sup>a</sup> |
| 7              |       |         | 30         | 90              |
| 8 <sup>b</sup> |       |         | 30         | 90              |
| 9              |       |         | 30         | 81              |
| 10             |       |         | 15         | 99              |
| 11             |       |         | 15         | 99              |
| 12             |       |         | 15         | 74              |
| 13             |       |         | 30         | 94              |
| 14             |       |         | 15         | 75              |
| 15             |       |         | 15         | 84              |
| 16             |       |         | 15         | 92              |

<sup>a</sup> The corresponding alcohol (12%) was also obtained. <sup>b</sup> Compound obtained with  $\text{Cp}_2\text{Zr}(\text{D})\text{Cl}$ . All other conditions remained the same.

withdrawing nature of the amide in the para position. This was confirmed by examining *p*-nitroacetophenone in the presence of the Schwartz reagent which, in fact, led to the corresponding 1-(*p*-nitrophenyl)-ethanol. Steric issues were also examined, (entries

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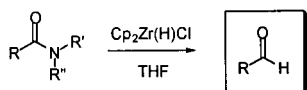
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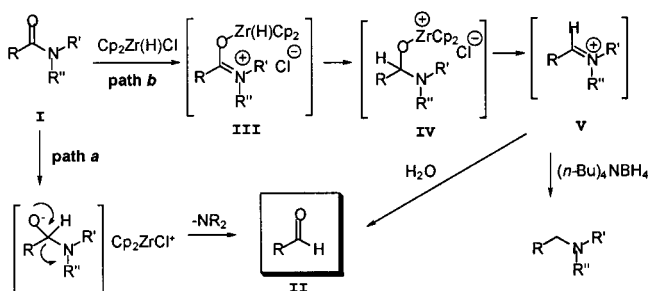
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## Scheme 1



## Scheme 2



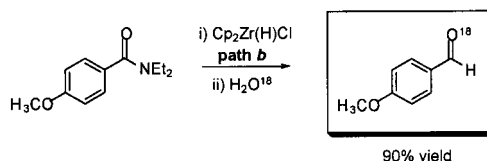
14 and 15) by reduction of the diisopropyl amide and the piperidinoamide. This was felt to be important, as some previous methods to reduce sterically demanding tertiary amides to aldehydes were unable to accomplish this task.<sup>8</sup> The yields, in these cases, were shown to be only slightly reduced. Of additional particular interest is the *selective chemical reduction of an tertiary amide in the presence of an ester functionality* (entries 11 and 12). This selective conversion has no general precedence to the best of our knowledge.<sup>9</sup> As seen in these examples,  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  under these conditions can reduce tertiary amides selectively, giving very good yields of the corresponding aldehydes in short reaction times.

A general procedure for this reaction is as follows: The substrate is taken into 5 mL of anhydrous THF under argon. This solution is then added to 1.5–2.0 equiv of  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  at room temperature under argon, which elicits the desired conversion within 15–30 min. Further workup by short path silica gel chromatography (hexanes:ethyl acetate) of the concentrated mixture affords the desired aldehydes in near quantitative yields.

Two major plausible routes through which this reaction may proceed are shown in Scheme 2. Following path *a*, **I** may react directly with the reagent via a direct hydride transfer proceeding through a tetrahedral intermediate, eventually losing the  $-\text{NR}_2$  group to give the aldehyde **II**. Alternatively, **I** can react via path *b* to give intermediate **III**, which can then be reduced (intermediate **IV**) to give eventually intermediate **V**. The iminium ion intermediate would be expected to be highly reactive, forming the aldehyde immediately in the presence of water.

The lack of over-reduction of the amide to the alcohol, even in the presence of excess (>2 equiv)  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  is supportive of path *b*, since it is well known that aldehydes will react with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  to give the corresponding alcohol.<sup>10</sup> To further examine this hypothesis, a tertiary amide was stirred with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  and subsequently treated immediately with tetrabutylammonium borohydride. If the reaction would proceed through

## Scheme 3



path *a*, the corresponding alcohol would be the expected product, and if path *b* were favored, the amine would be the expected product. The results from this experiment resulted in a 1:1 mixture of alcohol and amine. This results supports path *b* in that the formation of the alcohol can be explained by the presence of trace water, whereas the amine formation can only be explained via proposed path *b*. Furthermore, control experiments attempting the reduction of the tertiary amide in the presence of tetrabutylammonium borohydride did not lead to a reduced product as expected. Further literature precedence for path *b* comes from a study carried out by Ganem et al. where *secondary* amides were reduced to imines with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ .<sup>11</sup> This observation supports path *b*, in that the imine being formed from secondary amides would be neutral and fairly stable and, hence, not as reactive to water as the iminium ion intermediate, obtained in the reduction from tertiary amides. An additional interesting point related to the use of excess reagent is that no further reduction to the amine was observed.

Another experiment performed to further examine the proposed mechanism was carried out using a  $\text{H}_2\text{O}^{18}$  quench as the final step (Scheme 3), the premise being that if path *a* were followed, one would expect *no*  $\text{O}^{18}$  incorporation, whereas  $\text{O}^{18}$  incorporation should be expected if path *b* were followed. The reaction was carried out using an  $\text{H}_2\text{O}^{18}$  quench after reacting the substrate (*p*-methoxy-*N,N*-diethylbenzamide) and  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  for 5 min (1:1 mixture of  $\text{H}_2\text{O}^{16}$  and  $\text{H}_2\text{O}^{18}$ ). The resulting product was analyzed by  $^{13}\text{C}$  NMR and MS which showed incorporation of the label (carbonyl peaks at  $\delta$  191.25 and 191.22 in a 1:1 ratio, and a 1:1 ratio for the pairs  $m/z$  165, 163 ( $\text{M}^+$ ), and 164, 162, ( $\text{M}^+ - 1$ ).<sup>12</sup> Therefore, this experiment suggests that the proposed reaction path *b* is more likely than path *a*.

In summary, the reduction of tertiary amides to aldehydes via  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  shows several distinct advantages. The reaction requires very short reaction time (~15 min) and provides very high yields of the aldehydes with good chemoselectivity. Furthermore, the reaction does not require extensive workup procedures, nor does it require scrupulously dry conditions, if the aldehyde is the desired product. Additionally, substrate dependence is minimal, and it is therefore expected that this method will be useful for a wide variety of compounds. Further studies are currently underway to more fully examine the scope of this reaction.

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(12) Control experiments treating the aldehyde (*p*-methoxybenzaldehyde) with  $\text{H}_2\text{O}^{18}$  showed no incorporation even after 24 h of treatment; thus the background level of incorporation appears minimal.